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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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CAMPBELL & FLORES LLP
4370 LA JOLLA VILLAGE DRIVE
7TH FLOOR
SAN DIEGO, CA 92122

EXAMINER	
GOLDBERG, JEANINE ANNE	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/024,450	HUANG ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed September 17, 2004. Currently, claims 17-23.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.

3. Any objections and rejections not reiterated below are hereby withdrawn.

A. The 102(a) rejections have been withdrawn in view of the declarations filed 9/17/04. The Katz type declaration for the PNAS reference is sufficient. With respect to the Piao reference where Chadwick is not a named author, the declaration has been deemed sufficient in view of Ex parte Magner, Long, Ellis, and Grinstead (133 USPQ 404).

Priority

4. This application claims priority to provisional application 60/256,582, filed December 19, 2000.

Maintained Rejections

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 17-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining MSI status of a colorectal tumor, a gastric tumor and an endometrial tumor, comprising determining in the tumor the number of adenosine (A) nucleotides in a poly(A) tract located at positions 4393-4400 of SEQ ID NO: 3 or 4582-4590 of SEQ ID NO: 3, where a decrease of one or two adenosine nucleotides in said poly(A) tract indicates that the tumor is MSI-positive, does not reasonably provide enablement for a method of determining MSI status of any tumor by determining the number of adenosine nucleotides in any poly(A) tract of a RIZ nucleic acid where any abnormality is indicative of MSI-positive tumors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a method of determining MSI status of a tumor, comprising determining in said tumor the number of adenosine (A) nucleotides in a poly(A) tract of a RIZ nucleic acid molecule wherein an abnormal number of adenosine

nucleotides in said RIZ poly(A) tract indicates the tumor is MSI-positive. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims encompass a method of determining the MSI status of any tumor using any poly(A) tract in RIZ using any abnormality in the number of adenosine nucleotides of the tract.

The unpredictability of the art and the state of the prior art

The art teaches that reliable studies suggest there is a great difference in the observed frequency from one marker (i.e. one dinucleotide compared to a similar dinucleotide) to another and from one type of cancer to another (e.g., bladder cancer versus lung cancer) (see Boland et al. (Cancer Research, Vol. 58, pages 5248-5257, November 1998)). Boland teaches there are two types of noncolonic non-HNPCC tumors that display elevated frequencies of MSI. The first group is found in gastric, endometrial which has a similar phenotype to MSI in colorectal cancer and displays instability at mononucleotide markers and to a lesser degree at larger repeats (page 5253, col. 2). The second group of noncolonic non-HNPCC tumors display elevated frequencies in non-HNPCC tumors of different types such as lung, bladder and head/neck. Each of the cancers described in the instant specification are within the first group.

The art teaches detection of a A8 and an A9 poly(A) tract in RIZ as indicative of colorectal, gastric and endometrial tumors. Chadwick teaches sequence analysis

revealed frequent frameshift mutations of the RIZ gene. The mutations consisted of 1- or 2-bp deletions of a coding (A)8 or (A)9 tract and were confined to microsatellite-unstable colorectal tumors, being present in 9 of 24 (37.5%) primary tumors (abstract). The coding sequence of RIZ showed hypermutable tracts of (A)8 and (A)9 in exon 8 of RIZ gene. In 9/24 (37.5%) of the MSI(+) HNPCC tumors, frameshifts were found in either the A8 or A9 tract. None of the 23 tested MSI(-) sporadic colorectal cancers contained mutation in either of the polyadenosine tracts indicating that these regions were mutational hotspots in MSI(+) tumors only (page 2665, col. 2). As seen in Figure 3, Chadwick teaches 1-bp or 2-bp deletions.

Moreover, Piao et al. (Cancer Research, Vol. 60, pages 4701-4704, September 2000) teaches studying RIZ mutations in sporadic cancers with microsatellite instability. Frameshift mutations in the two coding polyadenosine tracks of RIZ were found in 19/40 (48%) gastric carcinomas, 6/18 (33%) endometrial carcinomas, 14/51 (26%) of colorectal carcinomas and 7/13 (54% cell lines) (abstract)(limitations of Claims 22-23). Piao teaches using primers for the A8 and A9 tract to amplify the region and sequenced (page 4702-4703)(limitations of Claim 18-19). No mutations in the A8 or A9 track were found in 70 MSI (-) gastric carcinomas. Piao teaches that 1bp and 2bp deletions were observed (see Figure 1)(limitations of Claim 21).

Guidance in the Specification and Working Examples

The specification teaches that a scan of RIZ1 cDNA sequence revealed two potentially hypermutable polyadenosine tracts within its coding region in exon 8: one A8 tract at residues 4393-4400 of SEQ ID NO: 3, and one A9 tract at residues 4582-4590 of SEQ ID NO: 3.

The specification analyzes the poly(A)8 and 9 tracts and 9/24of MSI(+) HNPCC tumors contain a frameshift mutation. None of the 23 tested MSI(-) sporadic colorectal cancers contained mutation in either polyadenosine tract (page 25).

The specification analyzes other known mononucleotide tracts in other genes and frameshifts in these tracts were completely absent in the MSI(+) tumors.

Example II provides an analysis of frameshift mutations in poly(A) tracts in gastric cancers, endometrial cancers and colorectal cancers (page 30). RIZ mutations were detected in 19/40 (48%) of gastric cancers; 6/18 (33%) endometrial cancers; and 14/51 (26%) of colorectal cancers (page 31).

The specification discusses 1bp deletion and 2bp deletion (page 32). The specification fails to describe any additional abnormalities.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since determination of additional tumors, additional poly(A) tracts and additional abnormalities are encompassed by the instant claims. The specification teaches the presence of deletions of 1bp or 2bp within the polyadenosine tracts within its coding region in exon 8: one A8 tract at residues 4393-4400 of SEQ ID NO: 3, and one A9 tract at residues 4582-4590 of SEQ ID NO: 3. The specification does not provide for any abnormality. The specification fails to provide any guidance as to the determination of MSI status for an increase in adenosine number. The specification fails to provide any evidence that the poly(A)8 and 9 tracts gain adenosine and are indicative of MSI status. Further, the only abnormalities discussed are 1bp or 2bp deletions. Therefore while one could conduct additional experimentation to determine whether, e.g. increase in numbers of adenosine might be associated with, e.g. MSI status in all tumors, the outcome of such

research cannot be predicted, and such further research and experimentation are both unpredictable and undue.

Moreover, the prior art teaches that there are two general types of tumors that display elevated frequencies of MSI. The instant specification appears to teach gastric, colorectal and endometrial which are all common to the first group. The first group is also characterized by mononucleotide makers which is claimed. There is not indication that the poy(A) tracts would be predictive of those cancers which are typically classified in the second group, such as lung, bladder and head and neck cancer. Because the art clearly provides a categorization between a two groups of cancers and the markers which allows for determination of MSI status, it is unpredictable that any of the cancers within the second group of tumors would be associated in the same manner as the first group. The skilled artisan would be required to perform additional experimentation as to whether abnormalities of any variety including 1bp and 2bp deletions in the poly(A) tracts would be associated with lung, bladder, head and neck cancers, for example.

Finally, the are drawn to any poly(A) tract in a RIZ nucleic acid molecule. The specification teaches scanning the RIZ1 cDNA sequence which revealed two potentially hypermutable polyadenosine tracts within its coding region in exon 8: one A8 tract at residues 4393-4400 of SEQ ID NO: 3, and one A9 tract at residues 4582-4590 of SEQ ID NO: 3. It is unpredictable whether the RIZ2 cDNA comprises any poly(A) tracts or whether the genomic DNA of RIZ comprises any poly(A) tracts. In the event that the skilled artisan identified an additional poly(A) tract, the skilled artisan would be required to perform additional experimentation to determine whether variations in the tract are related to MSI status. As noted above, while one could conduct such additional experimentation, the outcome of such research can not be predicted, and such further research and experimentation are both unpredictable and undue. This would require

inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability in the art is high, the specification provides one with no written description or guidance that leads one to a reliable method of determining MSI status. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of any working examples and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The response traverses the rejection. The response asserts that the claimed invention may be performed without undue experimentation. The response asserts that if it is merely routine, the claims are enabled (page 8 of response filed 9/17/04). The response asserts, "that there are different RIZ nucleic acids and more than two poly(A) tracts within each RIZ nucleic acid are material" (page 11 of response filed 9/17/04).

This argument has been thoroughly reviewed, but is not found persuasive because the claims remain drawn to a method of detecting the number of any poly(A) tract and determining the number of adenosine nucleotides wherein abnormal numbers of adenosine are indicative of MSI-positive tumors. The specification describes two specific poly(A) tracts. The specification teaches that a scan of RIZ1 cDNA sequence revealed two potentially hypermutable polyadenosine tracts within its coding region in exon 8: one A8 tract at residues 4393-4400 of SEQ ID NO: 3, and one A9 tract at residues 4582-4590 of SEQ ID NO: 3. Upon quick visual inspection of SEQ ID NO: 3, there are over six additional poly (A) tracts. The RIZ1 of SEQ ID NO: 3 comprises a polyA(6) tract at position 272 of SEQ ID NO: 3; a polyA(6) tract at 262 of SEQ ID NO: 3; a polyA(7) tract at position 310 of SEQ ID NO: 3; a polyA(6) tract at position 640 of SEQ ID NO: 3; a polyA(6) tract at 2434 of SEQ ID NO: 3; a polyA(6) tract at position 3715 of SEQ ID NO: 3, for example. As argued above, in the event that the skilled artisan identified an additional poly(A) tract, the skilled artisan would be required to perform additional experimentation to determine whether variations in the tract are related to MSI status. Thus, the skilled artisan would be required to perform additional experimentation which is unpredictable to determine whether each of these additional polyA tracts in RIZ are associated with MSI status. As stated above, Boland teaches that reliable studies suggest there is great difference in the observed frequencies from one marker to another (i.e. one dinucleotide compared with a similar dinucleotide)(page 5256, col. 1). Thus, it is unpredictable that every polyA tract within RIZ is associated with MSI status. The skilled artisan would be required to analyze each of the polyA

tracts found in each of the RIZ's to determine whether they are associated with MSI instability prior to determining whether a particular tumor is MSI positive. The art teaches the unpredictability between one marker to another and teaches that certain markers should not be used. Thus, the association of two particular markers within RIZ is not representative of an association between all polyA tracts absent further unpredictable experimentation.

The response asserts that in order to predict the MSI status of a tumor, the person of skill in the art would need only determine the number of adenosine (A) nucleotide in poly(A) tract of a RIZ nucleic acid molecule in said tumor. This argument has been thoroughly reviewed, but is not found persuasive because MSI status of a tumor may be established only after an association has been shown. Thus, for, the two polyA tracts one A8 tract at residues 4393-4400 of SEQ ID NO: 3, and one A9 tract at residues 4582-4590 of SEQ ID NO: 3, the determination of loss of 1 or 2 bp as indicative of MSI status has been shown to be associated with certain tumor MSI status. However, for the claim as broadly as written, determining the tumor MSI status based upon MSI would require further experimentation to establish an association prior to the "routine assay" to perform a determination on particular tumors.

The response asserts that "an abnormal number of adenosine nucleotides in the poly(A) tract of RIZ indicates to the person of skill in the art that the tumor is predicated to be MSI(+)" (page 9 of response filed 9/17/04). This argument has been thoroughly reviewed, but is not found persuasive. As discussed in the rejection above, the specification fails to provide any guidance as to the determination of MSI status for an

increase in adenosine number. The specification fails to provide any evidence that the poly(A)8 and 9 tracts gain adenosine and are indicative of MSI status. Further, the only abnormalities discussed are 1bp or 2bp deletions. Therefore while one could conduct additional experimentation to determine whether, e.g. increase in numbers of adenosine might be associated with, e.g. MSI status in all tumors, the outcome of such research cannot be predicted, and such further research and experimentation are both unpredictable and undue. The specification and the art fail to provide any guidance as to the value of determining an abnormality outside the two discussed in the specification. The status of the art is such that many neutral alleles occur in populations. Thus, it is unpredictable that any variation in deletion or insertion of an A at a polyA tract is indicative of positive MSI status.

The response asserts that a high degree of experimentation would not be required to predict the MSI(+) status of every type of tumor. The response asserts that the art teaches how to acquire a tumor sample, determine the number of adenosine nucleotides in a RIZ poly(A) tract and ascertain whether the number was normal. This argument has been thoroughly reviewed, but is not found persuasive. The examiner agrees that the steps of the method are routine once it is determined that a particular allele is associated with MSI status. However, in the instant case, the specification only teaches two polyA tracts in particular tumors which have been associated. As stated above, Boland teaches that reliable studies suggest there is a great difference in the observed frequency from one marker (i.e. one dinucleotide compared to a similar dinucleotide) to another and from one type of cancer to another (e.g., bladder cancer

versus lung cancer). Thus the art teaches that MSI status varies from one type of cancer to another. Thus it is unpredictable that all tumors act in accordance with each other. The skilled artisan would be required to establish an association between alleles and MSI status prior to being able to determine MSI status based upon polyA tracts. As supported by the art, this is unpredictable.

The response asserts "a relatively small number of cells may be tested and shown to have abnormal numbers of adenosine nucleotides in their poly(A) tracts: these would be predicted to be MIS(+)" (Page 10 of response filed 9/17/04). The response appears to focus on the routine nature of the testing. This is only one aspect of the Wands factors. The Wands factors also take into consideration the unpredictability. As established by the art, there is a significant degree of unpredictability between markers in cancers.

Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

6. No claims allowable.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J. Goldberg

Jeanine Goldberg
Patent Examiner
November 3, 2004